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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,411	KORNOWSKI ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,14-27,30-44,47-57,59-61,64-74,76-78,81-90 and 93-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,14-27,30-44,47-57,59-61,64-74,76-78,81-90 and 93-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/16/02;11/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Remarks, filed 02/20/04 is acknowledged. Applicant has not presented any arguments as to why restriction is improper. The requirement is still deemed proper and is therefore made FINAL. Applicant has cancelled claims 10, 11, 13, 28, 29, 45, 46, 62, 63, 79, 80, 91, 92 and 97-102. The pending claims are 1-9, 12, 14-27, 30-44, 47-61, 64-78, 81-90 and 93-96.

Claim Objections

Claims 14-17, 32-35, 49-52, 66-69, 83-86 and 95-98 appear to be drawn to non-elected subject matter in that the claims read on methods involving gene therapy (i.e. "gene...[promoting] ...blood vessel formation"). In the interest of furthering prosecution, the claims will be considered insofar as reading on the elected invention (i.e. not involving gene therapy). Appropriate amendment is required to remove non-elected subject matter.

Claims 9, 19, 27, 41, 44, 61, 78 and 90 are objected to because of the following informalities: Claims 9, 27, 44, 61, 78 and 90 contain acronyms. It is improper to use acronyms without first defining the corresponding terms in the claims. Claim 19 appears to be missing a period.

Claims 39 and 41 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

As written the claims are drawn to injecting ABM anywhere (i.e. peripherally) in the body, where the parent claim is drawn to trans-epicardial or -endocardial injection. Therefore, while the parent claim is delimited to a particular site (i.e. heart), the dependent claims broaden the scope to any site (i.e. peripheral). Thus the dependant claims do not further limit the parent claim but instead confer a broadened scope.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 6, 14-17, 24, 31, 39, 41, 48, 82 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 6 recites the limitation "limb". There is insufficient antecedent basis for this limitation in the claim. It would be remedial to include the limitation "tissue" after limb.

Claims 14-17 are vague and indefinite, because as written the claims' metes and bounds are indefinite. The base claim is drawn to ABMs being administered in combination with a *selected* drug or protein, which may enhance ABM production of angiogenic growth factors, which are themselves *selected* to promote blood vessel formation. As written, it appears that two separate selections are occurring. Does Applicant mean that the drug or protein is "selected" to elicit production of a particular growth factor, which in turn has the desired effect?

Claim 24 recites the limitation "the limb". There is insufficient antecedent basis for this limitation in the claim.

Claim 31 recites the limitation "growing in culture". Base claim 19 does not provide sufficient antecedent basis for this limitation.

Claims 39 and 41 recite that ABM is injected "peripherally intramuscularly". The claims are dependent from claims that limit injection to trans-epicardial or trans-endocardial. Therefore as written, the claim confers vagueness and indefiniteness, as it is unclear how an injection can occur peripherally and cardially concurrently.

Claims 48, 82 and 94 are vague and indefinite, because as written it is unclear whether the conditioned medium is derived from the ABM cells, or is simply the medium *in which* ABM cells are grown. The term "derived from" is not defined in the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 1-9, 12, 14-27, 30-44, 47-57, 59-61, 64-74, 76-78, 81-90 and 93-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for direct administration of ABMs to the heart, does not reasonably provide enablement for all embodiments claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.**

The invention is directed to three separate embodiments, which are not enabled commensurate with the scope of the claims.

The particular embodiments are: ABM *administration* with respect to the tissue or target site, the type of *stimulation* to which ABMS are subjected and the desired functional *outcomes* to which the claims are directed.

The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. First, the broadest claims are drawn to administering ABMs anywhere in the body. (e.g. base claims 1, 19, 36, 53 and 70). More specific claims are directed to administering ABMs directly to heart or limb tissue. The disclosure is enabling for direct administration to the heart, but is not enabling for administration elsewhere.

Second, the broadest claims are drawn to stimulating ABMs ex vivo with any stimulant, or any form of energy. (e.g. claims 7-9, 25-26, 42-44, 59-61, 76-78 and 88-90). More particular claims are directed to stimulating ABMs by treatment with hypoxia and Monocyte Chemoattractant Protein 1(MCP-1), as well as other unrelated factors (e.g. G[C]-CSF, HIF-1, EPAS1). The disclosure is enabling for stimulation via hypoxia or MCP-1, but is not enabling for all stimulants.

Finally, the broadest claims are drawn to the methods for achieving a desired outcome, such as improving electrical pathway impairment in the heart where impairment can be from any cause, enhancing myocardial function no matter the cause or treating any atrial or ventricular condition. Furthermore the broadest composition claim is drawn to ABMs for treatment of any cardiac or myocardial condition. More particular claims are drawn to enhancing angiogenesis or promoting development of newly implanted myocardial cells. The invention, while enabled for methods of enhancing angiogenesis in the heart, is not enabled for other embodiments.

Nature of the invention. The invention encompasses methods and cells directed at administering ABMs from a patient to either heart, limbs or peripheral sites to achieve desired outcomes, which include angiogenesis, promoting myocardial cell implantation, improved electrical conductivity, improve myocardial function and treat an atrial or ventricular condition. The desired outcomes of the invention are predicated on natural characteristics of ABMs as potential sources of cytokines and cells involved in control of angiogenic processes, including presence of endothelial precursors.

State/Unpredictability of the art. The art of delivering autologous bone marrow cells (ABMs) to various sites in the body in hopes of eliciting therapeutic effects related to neovascularization is at a comparatively nascent stage of development. Bone marrow-derived transplantation experiments in animals have demonstrated the existence of bone marrow-derived cells capable of neovascularization. (e.g. Tao and Ma. Pathology, 2003; 35:6-13, at p. 8, col. 2, ¶ 2; see the entire reference). The animal models tested include the mouse, rat and pig model.

However, the mechanisms by which cell therapy confers clinical benefits are not well understood. (e.g. Perin et al. Circulation, 2003; 107 :2294-2302, at p. 2301, col. 2; see the entire

reference). Furthermore, there is a great deal of unpredictability in the art of ABMs cell therapy with respect to the target site for administration in order to achieve a desired outcome.

The proceeding discussion will address both methods and compositions drawn to achieving broadly claimed embodiments of improving any myocardial function in any myocardial condition, treating any atrial/ventricular condition, improving cardiac electrical conductivity in the heart in any related impairment of the same and promoting development of newly implanted myocardial cells. For example, there could be unpredictable outcomes, such as the potential fusion between postnatal cells (i.e. ABMs) and embryonic cells leading to hybrid cells with abnormal chromosome counts. Furthermore, cellular genetic changes can occur in ABMs subjected to prolonged culture. (Tao and Ma. p. 10, qcol. 2, ¶ 2). In addition, there is variability between different ABMs harvests, because of the possibility of multiple lineage-restricted cells in the starting culture. (Id. p. 10, col. 1, ¶ 4). In other words, there are sub-populations within a particular ABM harvest that could determine cellular differentiation, which in turn could affect production of cytokines that may affect angiogenesis. Therefore, a particular harvest may not necessarily impart the desired effect at all and the outcome may depend on the specific site of administration.

While ABM administration may result in angiogenesis, such a result does not necessarily translate into ameliorating *any* atrial, ventricular or myocardial impairment. Therefore, promoting neovascularization in myocardial tissue, where a lack of vascularization is not the cause of a particular disorder, would not necessarily improve electrical conductivity, improve myocardial function or any atrial/ventricular condition. In other words, the underlying myocardial condition may not involve ischemia, for which angiogenesis would more likely be a

treatment. For example, a disorder of the heart valves (e.g. heart murmur) is certainly a myocardial condition, if the claims are interpreted as broadly as reasonable.

Clearly, it cannot be suggested that ABM transplantation into the heart would treat or ameliorate such a myocardial condition. Highlighting a fundamental uncertainty in the art, is the determination that merely enhancing angiogenesis does not necessarily translate into improved contractility (i.e. electrical conductivity). (e.g. Stamm et al. Lancet, 2003 ; 361 :45-6, at p. 46, col. 2, last ¶; indicating improved myocardial perfusion through implied angiogenesis did not improve contractility). With respect to promoting a myocardial cell implantation, there are concerns with unpredictability that are not addressed, such as immune response or immune rejection. While the particular embodiment directed to promoting newly implanted myocardial cells in a patient (base claim 19), the obstacles against successful transplantation, would necessarily be part of the enablement issue. For example, if the immune response trumps any benefit derived from enhanced angiogenesis or even ABM cell differentiation, then the invention cannot be deemed enabled for the prescribed use.

In light of the foregoing discussion on outcome, it logically follows, that if the site of administration may determine the efficacy for a particular outcome, then non-targeted administration results in greater unpredictability. For example, administering ABMs peripherally in a limb with the objective of improving angiogenesis in infarcted cardiac tissue is a remote possibility, given the knowledge in the art and what is taught in instant specification. The reason being that ABMs administered systemically or peripherally intramuscularly will not necessarily populate a desired target site (i.e. infarct heart muscle). The art teaches that

transplantation or administration is direct, such as administration into the center of scar tissue. (e.g. Tomita et al. Circulation, 1999; 100(Supp II) :II-247–II-256; under Methods, p. II-248-9).

Indeed, the instant specification similarly teaches direct ABM administration into an ischemic myocardial site using a transendocardial injection catheter. (Spec. p. 16, Example 4). Moreover, the degree/amount of infarcted tissue may require administration of a greater number of ABMs, with unpredictable results. (e.g. Stamm et al. Lancet, 2003 ; 361 :45-6, at p. 46, col. 2; indicating patients may not be able to tolerate a large number of cells).

With respect to ABM stimulation, there is a substantial level of unpredictability. For example it is not known whether the ABMs acquire certain phenotypes before leaving the marrow or once they have entered the microenvironment. It logically follows, that if it the cell lineage is predetermined then treating a mixed population of ABMs with a stimulating factor may not achieve the desired outcome. It also follows, that administering ABMs to various organs or tissue may not necessarily achieve the desired outcome in one versus another site.

Even where for example, angiogenesis is achieved in a specific tissue (i.e. heart), it may not be achieved in the other tissue. In other words, cells would be unresponsive to stimuli because cellular differentiation or production of angiogenic factors may be dependant on the type of injury and the amount of cells available at a critical time after injury. (e.g. Tao and Ma, 2003, at p. 10, col. 2, ¶ 4; indicating the uncertainty as to whether ABMs contain committed stem cells or more primitive stem cells that have transdifferentiation ability).

Amount of guidance provided. There is some guidance provided with respect to direct administration of ABMs into infarcted heart tissue. However, there is no significant guidance

provided for administering ABMs elsewhere in a patient (e.g. ischemic limb). The claims are drawn to administering ABMs anywhere (i.e. peripherally) or most specifically in limbs.

For the skilled artisan to be able to practice the invention commensurate with the scope of the claims there would have to be significant guidance provided, because the administered cells may not populate the target site at all. Cells could enter the systemic system once administered locally, where they may randomly or selectively populate non-target cites, leading to unpredictable outcomes. Furthermore, as cell characteristics may be predetermined in the marrow prior to harvesting/culturing, once implanted the cells may not produce the desired effect of promoting neovascularization. Therefore, the skilled artisan would not have the requisite knowledge, for example, to inject ABMs in an arm or leg, while targeting cells to populate ischemic heart tissue. Nor would the artisan be enabled to practice the invention so as to achieve angiogenesis in damaged limb tissue in the limb itself, as all the guidance provided is directed to infarcted heart tissue, using direct administration.

Given the unpredictability and uncertainties outlined above, the skilled artisan would not know how to target ABMs for a particular site or for a particular outcome without undue, unpredictable experimentation.

In addition, while there is some guidance provided for stimulating ABMs with MCP-1 or subjecting cells to hypoxia, there is no significant guidance provided as to other claimed embodiments directed at stimulating ABMs (e.g. forms of energy, HIF-1, EPAS1 or [C]M-CSF). For the skilled artisan to practice the invention, guidance would be needed as to what other forms of energy or agents can be used to stimulate ABMs, with respect to the underlying aim of enhancing angiogenesis or other claimed outcomes. The specification refers prophetically to

ultrasound, RF, electromagnetic or laser energy (Spec. p. 5, ll.8-11), but does not provide any guidance.

For example, using sonic waves, the skilled artisan would not know the frequency, total output (e.g. Watts), duration or temperature at which to conduct the stimulation. At a certain threshold, depending on the source/type of energy, there could presumably be deleterious effects (e.g. temperature stress, shearing). Furthermore, stimulating cellular growth in culture would not necessarily translate into the cells producing the desired angiogenic factors *in vivo*, as the mechanisms involved in neovascularization involve a cascade of complex interactions. Regardless, there is no significant guidance provided as to using any form of energy (e.g. sound or light) to stimulate cells.

Number of working examples. There are working examples provided in a pig model system. However, the examples are limited to *direct administration* of ABMs to infarcted heart tissue, stimulating ABMs with MCP-1 or hypoxia and where the method is directed to effectuating enhanced angiogenesis in myocardial tissue.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention commensurate with the scope of the claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER